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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/743,800	04/03/2001	Olaf Wilhelm	100564-00045	3073

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EXAMINER	
LIU, HONG	
ART UNIT	**PAPER NUMBER**
1624	

DATE MAILED: 09/12/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/743,800	Wilhelm et al.
Examiner	**Art Unit**
Hong Liu	1624

– The MAILING DATE of this communication appears on the cover sheet with the correspondence address –

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 2-4, 8-13, 16, 17, and 19-25 is/are pending in the applica

4a) Of the above, claim(s) 10, 12, 13, and 17 is/are withdrawn from considera

5) ☒ Claim(s) 2-4, 8, 9, 11, 16, and 19-25 is/are allowed.

6) ☐ Claim(s) _____ is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirem

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 9
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 2-4, 8-13, 16, 17, 19-25 are pending in this application.

Election/Restriction

Applicants's election of Group I, claims 1-9, 14-16 and 18 is acknowledged. Applicants' arguments that Group I and II should be examined together are found persuasive. Claims in Groups I and II will be examined together. Claims 10, 12, 13, and 17 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 19, 2, 4, 8, 9, 11, 16, and 20-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for preparation and use of compounds wherein R1 is piperidine or piperazine, R2 is 2, 4, 6, trisubstituted phenyl, does not reasonably provide enablement for preparation and use of compounds wherein R1 and R2 are other than those functional groups specified above. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The nature of the invention in the instant application has claims which embrace a diversity of chemically and physically distinct compounds, wherein R1 can be an unsubstituted or substituted, heteroaromatic group, containing one or more heteroatoms, etc. While 4 or 5 compounds are disclosed, there is insufficient guidance for preparing additional "urokinase inhibitors" which would be effective since the cited examples are drawn to a homogenous group of compounds not remotely commensurate in scope to applicants' claims. Only compounds wherein R1 is piperazine, piperidine, R2 is 2, 4, 6, triisopropyl substituted phenyl have been made.

Furthermore, testing data is limited to a number of compounds not considered to be representative of all the possible compounds encompassed by the claims. Examples should be of sufficient scope as to justify the scope of the claim. However, the generic claims are much broader in scope than is represented by the testing. The definitions of the various R1 variable embrace many structurally divergent groups not represented at all in testing, since testing for the instant compounds is not seen in the specification. Markush claims must be provided with support in the disclosure when the "working examples' fail to include written description(s) which teach how to make and use Markush members embraced thereby in full, clear and exact terms. See In re Fouch, 169 USPQ 429.

This area of activity can be expected to be highly structure specific and unpredictable, as is generally true for chemically-based pharmacological activity. In view of the structural divergence in the claims, one skilled in the art could not reasonably extrapolate the activities of some of the claimed compounds to the other structurally divergent compounds embraced by the claims which

have not been tested. In cases directed to chemical compounds which are being used for their physiological activity, the scope of the claims must have a reasonable correlation to the scope of enablement provided by the specification. See In re Surrey 151 USPQ 724 regarding sufficiency of disclosure for a Markush group. No reasonable assurance has been made that the instant compounds as an entire class have the required activities needed to practice the invention. Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability" have been demonstrated to be sufficiently lacking in the instant case for the scope being claimed.

Furthermore, the instant specification provides no direction or guidance for how to use the disclosed (and claimed) compounds since there are no working examples of experimental data to demonstrate that the compounds in treating pemphigus, no guidelines for determination of dosage needed to when the compounds are used with radiolabels or with cytotoxic substance, and no teaching how the data provided permits the determination of an effective amount for treating these disorders,. Therefore, in view of the breadth of the claims, the chemical nature of the invention, the unpredictability of *in vitro* and *in vivo* correlation, the lack of working examples, and the lack of further guidance in how to use the claimed compounds and compositions to actually treat these disorders, it would require an undue amount of experimentation to use the claimed inventions.

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 19, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons apply:

2. 1). Claim 19 is vague and indefinite in that the metes and bounds of "any radicals," page 2, line 5 of the amendment, "a peptide residue, or a polypeptide residue," page 2, line 14, "functionalized alkyl" is unknown.

3. 2)."unsubstituted or substituted" throughout claim 19 is unclear as to the nature and number of substituent(s) intended. recited. Deletion of the word "general" is suggested.

3). The use of "heteroaliphatic ring" in the definition of R variables is unclear to the array of heteroatoms as well as nature of atoms as ring members. See In re Wiggins 179 USPQ 421 for certain terminology regarding heterocyclic ring systems. Also, the size of cycloalkyl, page 4, line 5, is not specified.

4. 4). Claim 25 is a substantial duplicate of Claim 3.

5). Regarding claim 19, the phrase "e.g." and "in particular" renders the claim indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 19, 2-4, 11, 16, 23, and 24 are rejected under 35 U.S.C. 102(a) as being anticipated by Wikstroem et al., Chem Abstract 132: 222869. The instantly claimed compounds read on the reference compound, see the enclosed copy of CAPLUS computer search report and the compounds.

Applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 19, 2-4, 11, 16, 23, and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wilkstroem et al. (CH 689611). The reference teaches a generic group of compounds which embraces applicant's instantly claimed compounds. See formula I, wherein R is OH, piperidine, piperazine, R1 is substituted aryl, etc. The compounds are taught to be useful as urokinase inhibitors. The claims differ from the reference by reciting a specific species and/or a more limited genus than the reference. However, it would have nevertheless been obvious to one skilled in the art at the time of the invention to be motivated to select any of the species of the genus taught by the reference including those instantly claimed, because the skilled chemist would have the reasonable expectation that any of the specie of the genus would have similar properties and, thus, the same use as taught for the genus as a whole, i.e., urokinase inhibitors. One of ordinary skill in the art would have been motivated to select the claimed compounds from the genus in the reference since such compounds would have been suggested by the reference as a whole. It has been held that a prior art disclosed genus of useful compounds is sufficient to render prima facie obvious a species falling within a genus. See *In re Susi*, 440 F.2d 442, 169 USPQ 423, 425 (CCPA 1971), followed by the Federal Circuit in *Merck & Co. V. Biocraft Laboratories*, 847 F.2d 804, 10 USPQ 2d 1843, 1846 (Fed. Cir. 1989).

Claims 19, 2, 4, 16, 20-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sturzebecher et al. (J. Med. Chem., 1997 and WO 94/18185). Sturzebecher et al. teach a generic group of piperazides of 3-amidinophenylalanine derivatives (See formula in Table 4, P. 3094), in particular, where instant R1 is alkyl, etc. Compounds 2-6, 15, 17, and 27 differ only in the nature

of substituent for R_2, which is naphthyl. However, the compounds of the instant invention are generically embraced in view of the equivalence of naphthylsulfonyl, phenylsulfonyl, 4-tert-butylphenylsulfonyl. Thus, one of ordinary skill in the art would have been motivated to select the claimed compounds from the genus in the reference since such compounds would have been suggested by the reference as a whole. It has been held that a prior art disclosed genus of useful compounds is sufficient to render prima facie obvious a species falling within a genus.

Any inquiry concerning this communication should be directed to Examiner Hong Liu whose telephone number is (703) 306-5814. The examiner can normally be reached on Monday through Friday from 8:30 AM to 6:00 PM. If attempts to reach the examiner by the phone are unsuccessful, the examiner's supervisor, Mukund Shah can be reached at (703) 308-4716. The fax phone number for this group is (703) 308-4734 for "unofficial" purposes and the actual number for **official** business is (703) 308-4556. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose number is (703) 308-1235.

hl
September 10, 2002

Mukund Shah

Mukund Shah
Supervisory Patent Examiner
Art Unit 1624